Remarks/Arguments

Claims 39-43 are pending in this application. Although the Examiner has withdrawn prior rejections to the claims under 35 USC § 112, second paragraph, all claims remain rejected under 35 USC §101 utility requirement; the §112, first paragraph "how to use" requirement; and the 35 USC §102 and §103. In addition, the Examiner has raised a new objection/ rejection to Claim 39.

The present rejections to the claims are respectfully traversed.

Priority

The Examiner acknowledges that International Application PCT/US00/04414, filed February 22, 2000 supports the invention claimed in this application but asserts that Applicants cannot validly claim the priority of US provisional application Serial No. 60/099,803.

In addition, the Examiner adds on page 3, line 21 of the Office Action that "in the supplemental Application Data Sheet (ADS) filed April 21, 2003, Applicant is no longer claiming priority to provisional application Serial No. 60/099,803".

Applicants submit that priority has been claimed to PCT/US98/18824 filed September 10, 1998 in the above mentioned ADS and Applicants hereby rely on this application for the effective filing date of September 10, 1998. As will be apparent from the discussions below and the Declaration by Dr. Avi Ashkenazi filed under 37 C.F.R. §1.132, Applicants submit that the results of the gene amplification assay provide specific and substantial asserted utility for the claimed antibodies in this invention. Since this utility was disclosed in PCT/US98/18824, the claims pending are fully entitled to the priority of September 10, 1998.

Sequence Rule Compliance

Sequence listings submitted earlier failed to comply with the requirements of 37 C.F.R.1.821 through 1.825. Applicants hereby resubmit an amended sequence listing that are compliant with these above mentioned rules.

35§ 101 Utility / 35§ 112, First paragraph Rejections

The Examiner asserts on page 3 that the gene amplification data disclosed in Example 92 and Table 8 of the present application does not satisfy the utility requirement of 35 USC§ 101, for the polypeptide and further, that the gene amplification data does not satisfy the utility requirement of 35 USC§ 112, first paragraph, for the polypeptide. Citing Pennica *et al.,* the Examiner added that "no information is provided in the gene amplification data regarding the level of expression, activity, or role in cancer of the PRO214 polypeptide". The Examiner asserted that DNA amplification is not always associated with overexpression of gene product and concluded that, "the asserted diagnostic utility of the PRO214 polypeptide requires further research to identify or reasonably confirm a 'real world' context of use and the increased copy number of PRO214 DNA does not provide a readily apparent use for the PRO214 polypeptide".

Applicants respectfully disagree.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.*, submitted as Exhibit D of the Goddard Declaration filed with applicants' response to the prior Office Action. According to the quoted statement, "WISP-2 DNA genomic DNA was amplified in colon cancer cell lines and human colon tumors but RNA expression was reduced (2->30-fold) in 79% of the tumors." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility.

Enclosed is a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr Ashkenazi explains,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring

> of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, the PRO343 polypeptide and antibodies binding to it have a substantial specific utility, and the present rejection should be withdrawn.

Claim Rejections - 35 USC § 102(a)

Claim 39-43 are rejected under 35 U.S.C. § 102(a) as being anticipated by Ruben (dated 11/18/1999) which discloses an isolated polypeptide which, the Examiner alleges, is 97% identical to the amino acid of SEQ ID NO 109 of the present application.

As discussed above, the claims pending in this application are entitled to the effective filing date of September 10, 1998. The cited primary reference Ruben has a filing date of 11/18/1999 which is after the effective filing date (12/10/1998) of the present application. Hence, Ruben is not prior art under 102(b), and does not anticipate the present claims.

Hence Applicants request that this rejection be withdrawn.

Claim Rejections - 35 USC § 103

Claims 39 and 43 are rejected under 35 U.S.C. § 103 as being unpatentable over Koehrer (dated May 1999) which teaches a hypothetical protein that is at least 99% identical to SEQ ID NO: 109. The Examiner acknowledges that Koehrer does not teach an antibody that binds the hypothetical protein but says that making antibodies is obvious and can be done with reasonable expectation of success. Applicants respectfully traverse this rejection.

Again, as discussed above, since the effective filing date of the present application is September 10, 1998, Koehrer is not prior art since its effective date is after the effective filing date of the present application. Thus, Koehrer is not prior art under 35 U.S.C. §102 nor 35 U.S.C. §103(a).

Accordingly, the present claims are not obvious over Koehrer and Applicants request that this rejection be withdrawn.

New claim Rejection - 35 USC § 112, second paragraph

Claim 39 was held indefinite for reciting "specifically binds". The Examiner says that since the term "specifically binds" is not definitive from the specification, and the metes and bounds of the claim cannot be clearly set forth.

Since the art-recognized meaning of "specifically binds" is that the antibody specifically binds to a particular antigen and does not significantly cross-react with another antigen, the skilled artisan would clearly know the metes and bounds of the present claim.
Accordingly, the present rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C3). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 23, 2003

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